

WHAT IS CLAIMED IS:

1. Process for preparing stereoisomer-enriched 3-heteroaryl-3-hydroxypropanoic acid derivatives, comprising reacting
5 compounds of the formula (I),
$$\text{heteroaryl-CO-CH}_2\text{W} \quad (\text{I}),$$
in which
10 heteroaryl is a monocyclic or bicyclic aromatic radical having a total of from 5 to 10 ring atoms, where none, one or two ring atoms, selected from the group oxygen, sulphur and nitrogen, is present per cycle and one or two is present in the entire aromatic radical,
15 and where the monocyclic or bicyclic aromatic radical is optionally substituted, once, twice or three times, by radicals which are selected, in each case independently of each other, from the group hydroxyl, C₁-C₈-alkyl, cyano, COOH, COOM, where M is an alkali metal ion or a half equivalent of an alkaline earth metal ion, COO-(C₁-C₄-alkyl), O-(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, NH-(C₁-C₄-alkyl),
20 NO₂, fluorine, chlorine, bromine, C₁-C₄-fluoroalkyl, CONH₂ and CONH-(C₁-C₄-alkyl), and
25 W is C(O)YR¹_n, where Y is = oxygen and n is = 1 or Y is nitrogen and n is = 2, or
W is CN, and
30 R¹ are, in each case independently of each other, hydrogen, C₁-C₈-alkyl, C₄-C₁₀-aryl or C₅-C₁₁-arylalkyl or, when Y is nitrogen, the two radicals R¹ are together C₃-C₅ alkylene,

in the presence of microorganisms and/or cell preparations thereof, and

5 in the presence of water having a pH range of from 3 to 11,
based on 25°C.

to produce enantiomer-enriched compounds of the formula (II).

heteroaryl-CH(OH)-CH₂W (II),

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in which heteroaryl and W have the abovementioned meaning.

- 15 2. Process according to Claim 1, characterized in that, in the formulae (I) and (II), heteroaryl is a monocyclic aromatic radical which has a total of 5 or 6 ring atoms and in which one or two ring atoms is/are selected from the group oxygen, sulphur and nitrogen, and where the monocyclic aromatic radical contains no, one or two radical(s) which is/are selected, in each case independently of each other, from the group methyl, ethyl, n-propyl, isopropyl, cyano, COOH, COONa, COOK, COO-methyl, COO-ethyl, COO-tert-butyl, COO-phenyl, methoxy, ethoxy, dimethylamino, diethylamino, methyl-amino, ethylamino, fluorine, chlorine, NO₂, trifluoromethyl, pentafluoroethyl, heptafluoroisopropyl, CONH₂ and CONH-methyl.

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25 3. Process according to Claim 1, characterized in that, in the formulae (I) and (II), heteroaryl is 2-thiophenyl.

30 4. Process according to Claim 1, characterized in that, use is made of methyl 3-oxo-3-(2-thiophenyl)propanoate, ethyl 3-oxo-3-(2-thiophenyl)propanoate, methyl 3-oxo-3-(3-thiophenyl)propanoate, ethyl 3-oxo-3-(3-thiophenyl)propanoate, methyl 3-oxo-3-(2-

- furanyl)propanoate, ethyl 3-oxo-3-(2-furanyl)propanoate, methyl 3-oxo-3-(3-furanyl)propanoate, ethyl 3-oxo-3-(3-furanyl)propanoate, methyl 3-oxo-3-(2-pyridinyl)propanoate, ethyl 3-oxo-3-(2-pyridinyl)propanoate, methyl 3-oxo-3-(3-pyridinyl)propanoate, ethyl 3-oxo-3-(3-pyridinyl)propanoate, methyl 3-oxo-3-(4-pyridinyl)-
5 propanoate, ethyl 3-oxo-3-(4-pyridinyl)propanoate, 3-oxo-3-(2-thiophenyl)propanonitrile, 3-oxo-3-(3-thiophenyl)propanonitrile, 3-oxo-3-(2-furanyl)propanonitrile, 3-oxo-3-(3-furanyl)propanonitrile, 3-oxo-3-(2-pyridinyl)propanonitrile, 3-oxo-3-(3-pyridinyl)propanonitrile,
10 3-oxo-3-(4-pyridinyl)propanonitrile and N-(methyl)-3-oxo-3-(2-thiophenyl)propanamide.
- 15 5. Process according to Claim 1, characterized in that the microorganisms employed are bacteria, yeasts or fungi.
- 15 6. Process according to Claim 1, characterized in that the microorganisms employed are yeasts and fungi of the genera *Saccharomyces*, *Geotrichum*, *Candida*, *Pichia*, *Hansenula*, *Yarrowia*, *Rhizopus*, *Mortierella*, *Mucor*, *Sporotrichum*, *Rhodotorula*,
20 *Trichoderma*, *Aspergillus*, *Penicillium*, *Pullaria*, *Cunninghamella* and *Curvularia*.
- 25 7. Process according to Claim 1, characterized in that the sum of the concentrations of the compounds of the formulae (I) and (II) in the cell suspension is between 1 and 900 mM.
- 30 8. Process according to Claim 1, characterized in that the process is carried out in the presence of an organic solvent.
- 30 9. Process according to Claim 1, characterized in that the compounds produced are selected from the group consisting of methyl (S)-3-

hydroxy-3-(2-thiophenyl)propanoate, ethyl (S)-3-hydroxy-3-(2-thiophenyl)propanoate, methyl (S)-3-hydroxy-3-(3-thiophenyl)propanoate, ethyl (S)-3-hydroxy-3-(3-thiophenyl)propanoate, methyl (S)-3-hydroxy-3-(2-furanyl)propanoate, ethyl (S)-3-hydroxy-3-(2-furanyl)propanoate, methyl (S)-3-hydroxy-3-(3-furanyl)propanoate, methyl (S)-3-hydroxy-3-(2-pyridinyl)propanoate, ethyl (S)-3-hydroxy-3-(2-pyridinyl)thiophenyl)propanonitrile, (S)-3-hydroxy-3-(2-furanyl)propanonitrile, (S)-3-hydroxy-3-(3-furanyl)propanonitrile, (S)-3-hydroxy-3-(2-pyridinyl)propanonitrile, (S)-3-hydroxy-3-(3-pyridinyl)propanonitrile, (S)-3-hydroxy-3-(4-pyridinyl)propanonitrile and N-(methyl)-(S)-3-hydroxy-3-(2-thiophenyl)propanamide.

10. Process for preparing enantiomer-enriched compounds of the
15 formula (VI),

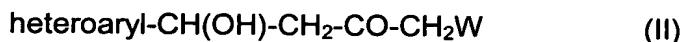


20 in which
heteroaryl has the same meaning as that given under formula
(I), and

25 R^2 and R^3 are, in each case independently of each other,
hydrogen, C₁-C₈-alkyl, C₄-C₁₄-aryl or C₅-C₁₅-arylalkyl,
or the two radicals R² and R³ are together C₃-C₁₂-alkylene, comprising

30 in a step a),

converting compounds of the formula (I) in accordance with Claim 1, into enantiomer-enriched compounds of formula (II)



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where, in each case,

heteroaryl and W have the meanings mentioned under formula (I), and

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in a step b)

- i) when W is COOR¹ and R¹ is hydrogen, C₁-C₈-alkyl, C₄-C₁₀-aryl or C₅-C₁₁-arylalkyl,

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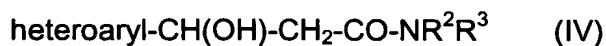
reacting the enantiomer-enriched compounds of formula (II) with amines of the formula (III)



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in which R² and R³ have the meaning mentioned under formula (VI), to give enantiomer-enriched compounds of the formula (IV)

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in which heteroaryl, R² and R³ have the previously mentioned meanings, or

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- ii) when W is CON(R¹)₂ and the R¹ radicals are in each case, independently of each other, hydrogen, C₁-C₈-alkyl,

C₄-C₁₀-aryl or C₅-C₁₁-arylalkyl, or the two R¹ radicals are together C₃-C₅-alkylene,

5 converting the enantiomer-enriched compounds of the formula (II) by reacting with amines of the formula (III), into enantiomer-enriched compounds of the formula (IV), and

10 iii) when W is CN, converting the compounds of the formula (II) directly, by aminolysis/hydrolysis, into compounds of the formula (IV), or converting initially hydrolysis, partial hydrolysis or mixed alcoholysis/hydrolysis, into compounds of the formula (V)

15 heteroaryl-CH(OH)-CH₂-CO-R⁴ (V)

in which heteroaryl has the meaning given under formula (I)

and R⁴ is OR¹ or NH₂, where R¹ has the abovementioned meaning, and

20 converting by amidation into enantiomer-enriched compounds of the formula (IV)

in a step c),

25 converting the enantiomer-enriched compounds of the formula (IV) by reduction, into enantiomer-enriched compounds of the formula (VI) having the abovementioned meaning.

15. Process according to Claim 10, characterized in that

in a further step d),

5 the enantiomer-enriched compounds of the formula (VI) are reacted, in the presence of base, with compounds of the formula (XI)



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in which

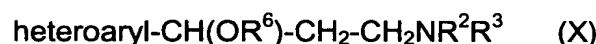
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R^6 is phenyl or naphthyl which is optionally substituted, once or more than once, by substituents which are selected, in each case independently of each other, from the group cyano, $\text{CO-(C}_1\text{-C}_{12}\text{-alkyl)}$, $\text{O-(C}_1\text{-C}_{12}\text{-alkyl)}$, $(\text{C}_1\text{-C}_{12}\text{-alkyl)}$, fluorine, chlorine, bromine and $\text{C}_1\text{-C}_{12}\text{-fluoroalkyl}$, and

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Hal is fluorine, chlorine, bromine or iodine,

to give enantiomer-enriched compounds of the formula (X),



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in which heteroaryl, R^2 and R^3 have the meaning given under formula (I) and R^6 has the meaning given under formula (XI).

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16. Process according to Claim 15, characterized in that (S)-N-methyl-3-(1-naphthalenyoxy)-3-(2-thienyl)propylamine and (R)-N-methyl-3-(1-naphthalenyoxy)-3-(2-thienyl)propylamine, or their ammonium salts, are prepared.

17. A process for preparing active compounds in medicaments selected from the group consisting of serotonin or noradrenaline uptake inhibitors, or as intermediates thereof comprising providing the compounds of Claim 15.

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18. A process for preparing active compounds in medicaments selected from the group consisting of serotonin or noradrenaline uptake inhibitors, or as intermediates thereof comprising providing the compounds of Claim 16.

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